a9 amprenavir, thereby assessing the effectiveness of nelfinavir, indinavir an amprenavir therapy.

REMARKS

Claims 1-12 are pending and under examination in the subject application. By this Amendment, applicants have amended claims 1, 4, 7 and 10. Accordingly, claims 1-12 are still pending in the subject application.

A marked up version of the amended claims and specification is attached hereto as **Exhibit A**, pursuant to the requirements of 37 C.F.R. §1.121.

In view of the amendments and arguments below, applicants maintain that the Examiner's rejections have been overcome, and respectfully request that they be withdrawn.

Formalities

Drawings

The Examiner objected to the drawings alleging that a description of individual figures 3a-e, 4a-e, and 5a-e must be in paragraph form under the Brief Description of the Drawings section.

In response, applicants respectfully note that although the Examiner objected to Figures 3a-e, Figures 3d-e do not exist in the subject application. With respect to the remaining figures, applicants have amended the specification to include paragraph descriptions of Figures 3a-c, 4a-e, and 5a-e.

The Examiner also stated that Figures P and Q were not described in paragraph form under the Brief Description of the Drawings section.

In response, applicants have amended the specification to include paragraph descriptions of theses Figures.

Specification

The Examiner objected to the disclosure stating that it contained an embedded hyperlink and/or other form of browser-executable code.

In response, applicants have deleted from the specification all hyperlinks and other forms of browser-executable code.

The Examiner objected to page 154 of the specification, alleging that the page was blank.

In response, applicants have cancelled page 154.

Provisional Claim Rejection Under 35 U.S.C. §101

The Examiner provisionally rejected claims 1-79 for allegedly claiming the same invention as that of claims 1-79 of co-pending Serial No. 09/663,458.

In response, applicants note that although the Examiner rejected claims 1-79, only claims 1-12 are currently under examination in the subject application. Applicants will consider canceling claims 13-79 and canceling claims 1-12 of the co-pending application once instant claims 1-12 are otherwise in condition for allowance.

Obviousness-Type Double Patenting Rejection

The Examiner provisionally rejected claims 1-12 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 98-112 and 114-117 of co-pending Application No. 09/766,344 in view of Patick et al.

In response, applicants respectfully traverse and maintain that the Examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest every element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

Applicants maintain that the '344 application and Patick et al., when combined, fail to teach each and every element of the claimed methods. Specifically, neither the '344 application nor Patick et al. provides the specific permutations of codon mutations set forth in the rejected claims. Moreover, Patick et al. teaches that the existence of mutations at codons 63, 10 and/or 20 in conjunction with a mutation at codon 82 *does not change* susceptibility to the drug Indinavir. This teaching is in stark contrast to the subject application which teaches that the existence of mutations at codons 63, 10 and/or 20 in conjunction with a mutation at codon 82 actually *decreases* susceptibility to the drug Indinavir.

Since the '344 application does not teach the specific permutations of codon mutations set forth in the rejected claims and Patick et al. actually teaches away from the subject invention, there would have been no motivation for the ordinary skilled artisan to combine the cited references or have a reasonable expectation of success. For this reason, applicants maintain that the rejected claims are not *prima facie* obvious over the '344 application in view of Patick et al.

In view of the above remarks, applicants maintain that claims 1-12 are not obvious over claims 98-112 and 114-117 in view of Patick et al.

Claim Rejection Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-12 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Specifically, the Examiner stated that claims 1-12 were unclear because it could not be determined if the instant invention involves a two-step assay or a one-step assay. Moreover, the Examiner stated that the intended meaning of claims 1-12 was not clear.

In response, applicants respectfully traverse, noting that the claims as amended clearly indicate the number of steps in the instant assays. Moreover, claims 1-12, as amended, are clearly directed towards methods for assessing the effectiveness of specific drug therapies based on determining the presence of mutations at specific codons in HIV protease-encoding nucleic acid.

In view of the above remarks, applicants maintain that claims 1-12 satisfy the requirements of 35 U.S.C. §112, second paragraph.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-12 under 35 U.S.C. §112, first paragraph, as allegedly not enabling any person skilled in the art to make or use the invention commensurate in scope with these claims.

Specifically, the Examiner stated that the specification does not provide enablement for some existent mutations at certain codons to denote an increase or decrease in drug resistance to a specific protease inhibitor or for the lack of mutations to indicate an increase in drug resistance.

In response, applicants respectfully traverse the Examiner's rejection, and contend that the instant claims are enabled by the specification. Specifically, the specification discloses a correlation between the existence of specific mutations at certain codons and susceptibility to specific drugs. The Examiner's attention is respectfully directed to the specification at page 126, line 23 to page 132, line 27, which is replete with data demonstrating the *decrease* in susceptibility to certain drugs correlative with mutations at certain specified codons. In addition, the Examiner is respectfully directed to the specification at page 32, line 26 to page 33, line 14, which provides data demonstrating the *increase* in susceptibility to certain drugs correlative with mutations at certain specified codons. Therefore, applicants maintain that the specification permits a person skilled in the art to practice the claimed methods.

Finally, the Examiner alleges that the specification does not describe the nature or characteristic of a codon mutation that would indicate resistance to a specific protease inhibitor. Therefore, the Examiner concludes that undue experimentation would be required to predict, based on condon sequence, the drugs to which a patient will be resistant.

In response, applicants respectfully traverse the Examiner's rejection. Applicants direct the Examiner's attention to the specification at page 25, line 11 to page 27, line 24, which states specific types of mutations that lead to changes in drug susceptibility. Applicants stress that the identity of these codons is set forth in the claims, and thus, no experimentation is required to determine their identities.

In view of the above remarks, applicants maintain that claims 1-12 satisfy the requirements of 35 U.S.C. §112, first paragraph.

Claim Rejections Under 35 U.S.C. §102(a)

The Examiner rejected claims 1-12 as allegedly anticipated by Patick et al.

In response, applicants respectfully traverse the Examiner's rejection. For Patick et al. to anticipate any of the rejected claims, it would have to teach each and every element thereof. This it fails to do.

Specifically, as set forth above, Patick et al. fails to teach the specific permutations of codon mutations set forth in the rejected claims, as well as their correlation with certain effects on drug susceptibility. Therefore, applicants maintain that Patick et al. does not anticipate the rejected claims.

In view of the above remarks, applicants maintain that claims 1-12 satisfy the requirements of 35 U.S.C. §102(a).

Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection and earnestly solicit allowance of the pending claims.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee, other than the enclosed $460.00 for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents Washington, D.C. 20231.

9/27/02

Alan J. Morrison Date
Reg. No. 37,399

Applicants : Neil T. Parkin and Rainer A. Ziermann
Serial No. : 09/591,899
Filed : June 12, 2000

Exhibit A

The paragraph beginning on page 7, line 34, has been replaced with the following paragraph:

As new protease inhibitors are developed, the ability of certain amino acid substitutions to confer resistance to the inhibitor is usually determined by several methods, including selection of resistant strains in vitro, site-directed mutagenesis, and determination of amino acid changes that are selected during early phase clinical trials in infected patients. While some amino acid substitutions are specifically correlated with resistance to certain protease inhibitors (see below), there is considerable overlap between sets of mutations implicated in resistance to all approved protease inhibitors. Many investigators have attempted to classify these mutations as either being "primary" or "secondary", with varying definitions. For example, some investigators classify as primary mutations which are predicted, based on X-ray crystallographic data, to be in the enzyme active site with the potential for direct contact with the inhibitor. (e.g. D30N, G48V, I50V, V82A/F/S/T, I84V, N88S, L90M). Secondary mutations are usually considered as being compensatory for defects in enzyme activity imposed by primary mutations, or as having enhancing effects on the magnitude of resistance imparted by the primary mutations (e.g. L10I/F/R/V, K20I/M/R/T, L24I, V32I, L33F/V, M36I/L/V, M46I/L/V, I47V, I54L/V, L63X, A71T/V, G73A/S/T, V77I, N88D). Lists of either being "primary" or "secondary", with varying definitions. For example, some investigators classify as primary mutations which are predicted, based on X-ray crystallographic data, to be in the enzyme active site with the potential for direct contact with the inhibitor. (e.g.

D30N, G48V, I50V, V82A/F/S/T, I84V, N88S, L90M). Secondary mutations are usually considered as being be in the enzyme active site with the potential for direct contact with the inhibitor. (e.g. D30N, G48V, I50V, V82A/F/S/T, I84V, N88S, L90M). Secondary mutations are usually considered as being compensatory for defects in enzyme activity imposed by primary mutations, or as having enhancing effects on the magnitude of resistance imparted by the primary mutations (e.g. L10I/F/R/V, K20I/M/R/T, L24I, V32I, L33F/V, M36I/L/V, M46I/L/V, I47V, I54L/V, L63X, A71T/V, G73A/S/T, V77I, N88D). Lists of al., Human Immunodeficiency Virus Reverse Transcriptase and Protease Sequence Database, Nucleic Acids Research 1999, 27(1), 348-352 [also accessible via the internet at http://www.viral-resistance.com/ or http://hivdp.stanford.edu/hiv/.]

The paragraph beginning on page 32, line 7, has been replaced with the following paragraph:

[Fig. 3] Figures 3a-3c
Examples of phenotypic drug susceptibility profiles. Data are analyzed by plotting the percent inhibition of luciferase activity vs. log10 concentration. This plot is used to calculate the drug concentration that is required to inhibit virus replication by 50% (IC50) or by 95% (IC95). Shifts in the inhibition curves towards higher drug concentrations are interpreted as evidence of drug resistance. Figure 3a shows the typical curve of drug susceptibility for the nucleoside reverse transcriptase inhibitor AZT. Figure 3b shows the typical curve of drug susceptibility for the non-nucleoside reverse transcriptase inhibitor efavirenz. Finally, Figure 3c shows the typical curve of drug susceptibility for the protease inhibitor

indinavir. A reduction in drug susceptibility (resistance) is reflected in a shift in the drug susceptibility curve toward higher drug concentrations (to the right) as compared to a baseline (pre-treatment) sample or a drug susceptible virus reference control, such as pNL4-3 or HXB-2, when a baseline sample is not available.

The paragraph beginning on page 32, line 26, has been replaced with the following paragraph:

[Fig 4] Figs. 4a-e

Phenotypic PRI susceptibility profile: patient 0732. A PCR-based phenotypic susceptibility assay was carried out giving the phenotypic drug susceptibility profile showing decreased susceptibility to nelfinavir and indinavir, and increased susceptibility amprenavir. Figure 4a shows a dose response relationship in subjects treated with saquinavir. Figure 4b shows a dose response relationship in subjects treated with indinavir. Figure 4c shows a dose response relationship in subjects treated with ritonavir. Figure 4d shows a dose response relationship in subjects treated with nelfinavir. Finally, Figure 4e shows a dose response relationship in subjects treated with amprenavir.

The paragraph beginning on page 33, line 5, has been replaced with the following paragraph:

[Fig 5] Figs. 5a-e

Phenotypic PRI susceptibility profile of a protease mutant generated by site-specific oligonucleotide-directed mutagenesis. A PCR-based phenotypic susceptibility assay was carried out giving the phenotypic drug susceptibility profile of a virus having substitutions at codons 63, 77,

and 88 (L63P, V77I, and N88s). The profile demonstrated resistance to both nelfinavir and indinavir, and increased susceptibility to amprenavir. Figure 5a shows a dose response relationship in subjects treated with saquinavir. Figure 5b shows a dose response relationship in subjects treated with indinavir. Figure 5c shows a dose response relationship in subjects treated with ritonavir. Figure 5d shows a dose response relationship in subjects treated with nelfinavir. Finally,Figure 5e shows a dose response relationship in subjects treated with amprenavir.

Claims 1,4, 7 and 10 have been amended as follows:

1. (Amended) A method for assessing the effectiveness of [protease antiretroviral] amprenavir therapy [of] in an HIV-infected patient comprising:
   (a) collecting a [plasma] biological sample from the HIV-infected patient; and
   (b) [evaluating whether the plasma sample contains nucleic acid encoding HIV protease having a mutation at codon 88; and] determining whether the biological sample contains nucleic acid encoding HIV protease having a mutation at codon 88, the presence of such nucleic acid in the sample indicating an increase in susceptibility to amprenavir, thereby assessing the effectiveness of amprenavir therapy in the patient.
   [(c) determining increased susceptibility to amprenavir.]

4. (Amended) A method for assessing the effectiveness of [protease antiretroviral] nelfinavir, indinavir and amprenavir therapy [of] in an HIV-infected patient comprising:
   (a) collecting a [plasma] biological sample from the HIV-

infected patient; and

(b) [evaluating whether the plasma sample contains nucleic acid encoding HIV protease having a mutation at codon 88 and additional mutations at codons 63 and/or 77 or a combination therof; and] determining whether the biological sample contains nucleic acid encoding HIV protease having (i) a mutation at codon 88 and (ii) a mutation at codon 63 and/or 77, the presence of such nucleic acid in the sample indicating a decrease in susceptibility to nelfinavir and indinavir and an increase in susceptibility to amprenavir, thereby assessing the effectiveness of nelfinavir, indinavir and amprenavir therapy in the patient.

[(c) determining decreased susceptibility to nelfinavir and indinavir and increased susceptibility to amprenavir.]

7. (Amended) A method for assessing the effectiveness of [protease antiretroviral] nelfinavir, indinavir and amprenavir therapy [of] in an HIV-infected patient comprising:

(a) collecting a [plasma] biological sample from the HIV-HIV-infected patient; and

(b) [evaluating whether the plasma sample contains nucleic acid encoding HIV protease having a mutation at codon 88 and additional mutations at codons 63, 77 and/or 46 or a combination therof; and] determining whether the biological sample contains nucleic acid encoding HIV protease having (i) a mutation at codon 88 and (ii) a mutation at codon 63, 77 and/or 46, the presence of such nucleic acid in the sample indicating a decrease in susceptibility to nelfinavir and indinavir and an increase in susceptibility to amprenavir, thereby assessing the effectiveness of nelfinavir, indinavir

and amprenavir therapy in the patient.

[(c) determining decreased susceptibility to nelfinavir and indinavir and increased susceptibility to amprenavir.]

10. (Amended) A method for assessing the effectiveness of [protease antiretroviral] nelfinavir, indinavir and amprenavir therapy [of] in an HIV-infected patient comprising:

(a) collecting a [plasma] biological sample from the HIV-HIV-infected patient; and

(b) [evaluating whether the plasma sample contains nucleic acid encoding HIV protease having a mutation at codon 88 and additional mutations at codons 63, 77, 46, 10, 20, and/or 36 or a combination therof; and] determining whether the biological sample contains nucleic acid encoding HIV protease having (i) a mutation at codon 88 and (ii) a mutation at codon 63, 77, 46, 10, 20 and/or 36, the presence of such nucleic acid in the sample indicating a decrease in susceptibility to nelfinavir and indinavir and an increase in susceptibility to amprenavir, thereby assessing the effectiveness of nelfinavir, indinavir and amprenavir therapy in the patient.

[(c) determining decreased susceptibility to nelfinavir and indinavir and increased susceptibility to amprenavir.]